REMARKS

This Amendment responds to the Office Action mailed on November 12, 2008. In the Office Action, the Examiner:

- rejected claims 1, 3, 5-11, 14-15, and 22 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement;
- rejected claims 1-2, 5 and 10 under 35 U.S.C. § 102(a) as being unpatentable over Tsimberidou *et al.* (Cancer Chemotherapy and Pharmacology (2002) 50:237-242, "Tsimberidou *et al.*");
- rejected claims 1-2, 5, 10-11, 14-15 and 22-31 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al* in view of Man *et al.* (WO 2001/34606, "Man *et al.*");
- rejected claims 3-4 and 7-9 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* in view of Man *et al.* and Alter *et al.* (Blood (1985) 66:373-379, "Alter *et al.*"); and
- rejected claim 6 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* in view of Man *et al.* and Canepa *et al.* (British Journal of Haematology (2001) 115:313-315, "Canepa *et al.*").

Claims 1-40 were pending. Claims 12-13, 16-21 and 32-40 were withdrawn from consideration by the Examiner. Claims 2, 4, 10, 12-14, 16-21, and 23-40 are canceled. Claims 1, 3 and 22 are amended to replace the "selective cytokine inhibitory drug" by "cyclopropanecarboxylic acid {2-[(1*S*)-1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}-amide"; and to recite that the myeloproliferative disease is polycythemia rubra vera, primary thrombocythemia, chronic myelogenous leukemia or agnogenic myeloid metaplasia. The amendments are supported by the specification, for example, at page 22, lines 24-26; and page 7, lines 24-31. Claims 1 and 3 are further amended to add the term "managing" and the amount of the compound "from about 5 mg to about 50 mg per day". The amendments are supported by the specification, for example, original claims 2 and 4; and at page 39, lines 12-15, and at page 36, lines 15-17. Claims 5, 6, 7, 8, 11 and 15 are amended to correct their dependency after the cancellation of claims 2, 4 and 14. New claims 41-51 are added. Claim 41 is supported by the specification, for example, at page 22, lines 24-26, and claims 14-15. Claims 42-43 are supported by the specification, for example, at page 39, lines 24-26. Claims 44-46 are supported by the

specification, for example, at page 39, lines 12-15; and at page 36, lines 15-17. Claims 47-49 are supported by the specification, for example, at page 33, lines 20-23; and at page 6, line 23 to page 7, line 22. Claim 50 is supported by the specification, for example, at page 22, lines 24-26; and at page 32, line 1. Claim 51 is supported by the specification, for example, at page 22, lines 24-26; and at page 28, line 21. No new matter is added by this Amendment. After this Amendment, the pending claims are 1, 3, 5-9, 11, 15, 22, and 41-51.

I. The Rejection of Claims 1, 3, 5-11, 14-15, and 22 under 35 U.S.C. § 112, First Paragraph Should Be Withdrawn

On page 2 of the Office Action, the Examiner rejected claims 1, 3, 5-11, 14-15, and 22 under 35 U.S.C. § 112 , first paragraph as allegedly failing to comply with the enabling requirements of the specification. The Examiner alleged that the specification, while being enabling for a method of managing a myeloproliferative disease, does not reasonably provide enablement for a method of preventing and/or treating a myeloproliferative disease comprising administering a therapeutically or prophylactically effective amount of a selective cytokine inhibitory drug. (*See* page 3 of the Office Action). Applicant respectfully disagrees.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation. *U.S. v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). The test is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is not undue. *See*, *In re Angstadt*, 190USPQ 214, 219 (C.C.P.A. 1976). The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. MPEP § 2164.04, (citing *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993)). Furthermore, "[a] specification disclosure...must be taken as being in compliance with the enablement requirement...unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *Id.* (emphasis added). Thus, the burden is on the Examiner to provide evidence showing that one of ordinary skill in the art would have some basis to reasonably doubt Applicants' asserted utility on its face. *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995). Moreover, "not everything necessary to practice the invention need be disclosed. All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art." MPEP § 2164.08 (emphasis added).

Claims 1, 3 and 22 have been amended to delete "preventing" and to recite, *inter alia*, methods of treating or managing a myeloproliferative disease, by administering cyclopropanecarboxylic acid {2-[(1*S*)-1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}-amide; wherein the myeloproliferative disease is polycythemia rubra vera, primary thrombocythemia, chronic myelogenous leukemia or agnogenic myeloid metaplasia.

Applicant respectfully submits that the specification discloses at page 1, lines 9-24 that myeloproliferative disease (MPD) refers to a group of disorders characterized by clonal abnormalities of the hematopoietic stem cells (myeloid, erythroid, and platelet cells); these disorders include polycythemia rubra vera (PRV), primary thromobocythemia (PT), chronic myelogenous leukemia (CML) and agnogenic myeloid metaplasia (AMM); and these disorders are grouped together, because the disease may evolve from one form into another and because hybrid disorders are commonly seen. Also, see, e.g., *Current Medical Diagnosis & Treatment*, pp. 499 (37th ed., Tierney *et al.* ed., Appleton & Lange, 1998); *Cecil Textbook of Medicine*, pp. 922 (20th ed., Bennett and Plum ed., W.B. Saunders Company, 1996). Each of the PRV, PT, CML and AMM are further described at page 1, line 25 to page 2, line 27.

The specification clearly discloses that the myeloproliferative diseases can be treated with the recited compound. *See*, for example, page 6, lines 23-31; page 22, line 17 to page 23, line 5; and page 24, lines 17-23 of the specification. The recited compound is ready available from Celgene Corp., Warren, NJ. *See*, for example, page 22, lines 17-21. Alternatively, the instant compounds can be prepared by a procedure similar to those for Examples 18-20 in pages 66-68 of U.S. Provisional Application No. 60/454,155, which is incorporated into this application by reference. See page 18, lines 25-27. The specification also discloses that the myeloproliferative diseases can be treated with a second active ingredients together with the recited compound. *See*, for example, pages 25-32; and page 34, line 6 to page 35, line 6 of the specification. The specification also discloses various methods of treating or managing the claimed diseases and the methods of administration, amounts of the compound and dosage forms to be used in treating the specified disease. *See*, for example, pages 32-44 of the specification.

The specification further discloses on pages 10-11, that the compounds described therein are potent TNF-α inhibitors and PDE4 inhibitors. As further described and exemplified in the application on pages 45-46, the selective cytokine inhibitory compound shows activity as a potent inhibitor of TNF-α production following LPS-stimulation of human PBMC and human whole blood. Applicant respectfully submits that at the time of effective filing date of the application, it was reported in the literature that TNF-α is implicated in MPD. For example, an article by Kastritis *et al.*, provided herewith, describes that myelofibrosis with myeloid metaplasia (MMM), a MPD, is mediated by cytokines such as TNF-α, and lenalidomide (*i.e.*, 3-(4-amino-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione) can be used to treat MPD such as MMM. *See* for example, page 505 of Kastritis *et al.* Applicant respectfully submits that Kastritis *et al.* provides a correlation between inhibition of TNF-α and treatment of MPD, and that the Office Action at page 10 admits that TNF-α is involved in the pathophysiology of MPD, refereing to Tsimberidou *et al.* Therefore, there is sufficient rebuttal evidence to prove that the pending claims are indeed enabled. *(See e.g. In re Brana*, 51 F.3d at 1566-67 (Claims held to be enabled, in part, because "[e]ven if the PTO met its initial burden...applicants proffered sufficient evidence to convince one of skill in the art of the asserted utility.")). Applicant respectfully submits that the Examiner has not provided any evidence showing that one of ordinary skill in the art would have some basis to reasonably doubt Applicant's asserted utility on its face. *In re Brana,* at 1566.

Hence, given the guidance in the specification coupled with information known to those skilled in the art, Applicant respectfully submits that the specification provides sufficient guidance necessary to treat the claimed diseases, and that the specification does provide sufficient guidance to enable one of skill in the art to practice the claimed invention without undue experimentation.

For at least the foregoing reasons, Applicant respectfully submits that all of the pending claims are enabled and requests that this rejection be withdrawn.

II. The Rejection of Claims 1-2, 5 and 10 under 35 U.S.C. § 102(a) Should Be Withdrawn

On page 8 of the Office Action, the Examiner rejected claims 1-2, 5 and 10 under 35 U.S.C. § 102(a) as being unpatentable over Tsimberidou *et al.* (*Cancer Chemotherapy and Pharmacology* (2002) 50:237-242). Applicant respectfully disagrees.

Claims 2 and 10 have been canceled and claims 1 and 5 have been amended. The currently amended claim 1 recites, *inter alia*, a method of treating specific myeloproliferative diseases (MPD) using cyclopropanecarboxylic acid {2-[(1*S*)-1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}-amide which was recited in original claims 14-15. Applicant respectfully appreciates that original claims 14-15 reciting the instant compound were not rejected. Without acquiescing to the rejection and solely to promote allowance of this case, Applicant has amended the rejected claims to recite the instant compound.[1] Thus, this rejection is now moot and should be withdrawn.

III. The Rejection of Claims 1-2, 5, 10-11, 14-15 and 22-31 under 35 U.S.C. § 103(a) Should Be Withdrawn

On page 10 of the Office Action, the Examiner rejected claims 1-2, 5, 10-11, 14-15 and 22-31 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* in view of Man *et al.* (WO 2001/34606). Applicant respectfully disagrees.

The Examiner alleged that Tsimberidou *et al.* teaches (1) a method of treating agnogenic myeloid metaplasia (AMM) with Etanercept; (2) that signs of clinical improvement were noted in some patients, particularly in those with AMM; (3) that TNF-alpha is involved in the pathophysiology of myeloproliferative disorders; and (4) that the patients being treated had refractory AMM. *See* page 10 of the Office Action. The Examiner also alleged that Man *et al.* teaches a compound which appears to be the claimed "Compound A", *i.e.*, cyclopropanecarboxylic acid {2-[(1*S*)-1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}-amide, as Examples 55, 57 and 58; and that the compounds of Man *et al.* are useful for the treatment of disease states mediated by TNF-alpha. *See* the first paragraph at page 11 of the Office Action. The Examiner further alleged that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Tsimberidou *et al.* and Man *et al.* so as to substitute Etanercept as taught by Tsimberidou *et al.* for the TNF-alpha inhibitor taught by Man *et al.* *See* the second paragraph at page 11 of the Office Action.

[1] Applicant will address the arguments as to the differences of the claimed invention from Tsimberidou *et al.* in the following section.

Claims 2, 10, 14, and 23-31 have been canceled and therefore, the rejection of claims 2, 10, 14, and 23-31 is moot.

Claims 1 and 22 have been amended to recite, *inter alia*, a method of treating a myeloproliferative disease comprising administering to a patient cyclopropanecarboxylic acid {2-[(1*S*)-1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}-amide; wherein the myeloproliferative disease is polycythemia rubra vera, primary thrombocythemia, chronic myelogenous leukemia or agnogenic myeloid metaplasia.

The current standard of obviousness takes into account (1) whether there would have been a "reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does;" and (2) whether the combination of elements would have yielded "predictable results" *i.e.*, whether there would have been a reasonable expectation of success. (*See e.g., PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d at 1342, 1360 (Fed. Cir. 2007) ("The burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, and would have had a reasonable expectation of success in doing so.") (emphasis added, internal quotations omitted)).

With regard to the instant case, Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness. Specifically, Applicant respectfully submits the following:

(1) The cited references would not have provided any reason to combine their teachings so as to substitute Etanercept with isoindoline derivatives of Man *et al.*, much less the instant compound, cyclopropanecarboxylic acid {2-[(1*S*)-1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}-amide; and

(2) The cited references would not have provided the legally required reasonable expectation of success.

1. The cited references would not have provided any reason to combine their teachings so as to substitute Etanercept with isoindoline derivatives

The Examiner fails to establish the key novel and inventive elements of the instant claims: the administration of cyclopropanecarboxylic acid {2-[(1*S*)-1-(3-ethoxy-4-methoxy-

phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}-amide ("instant compound") for the treatment of specific MPD at the narrow dose range of from about 5 to about 50 mg per day. Indeed, while the instant claims narrowly focus on the administration of a specific compound for the treatment of specific MPD at a specific dose, the Examiner fails to establish that each of these claim limitations is taught or suggested in the prior art. *See, e.g. In re Ochiai*, 71 F.3d 1565, 1572. (Fed. Cir. 1995)) (PTO must establish "that the invention as claimed in the application is obvious over cited prior art, based on the specific comparison of that prior art with claim limitations.").

Further, the Examiner's rejection is flawed because it relies on the false assumption that there is a motivation to combine the teachings of Tsimberidou *et al.* and Man *et al.* so as to substitute Etanercept as taught by Tsimberidou *et al.* for the isoindoline derivatives taught by Man *et al.* Not only the cited references would not have provided any reason to combine their teachings for the treatment of myeloproliferative disease, but also the cited references have provided reasons as shown below not to combine their teachings so as to substitute Etanercept of Tsimberidou *et al.* with the isoindoline derivatives of Man *et al.*, much less the instant compound.

Man *et al.* discloses in page 9, lines 18-28 that the isoindoline derivatives can be used to treat numerous possible disease states mediated by TNF-alpha, which, however, do **not** include polycythemia rubra vera (PRV), primary thromobocythemia (PT), and chronic myelogenous leukemia (CML), agnogenic myeloid metaplasia (AMM), or any other myeloproliferative disease (MPD). Man *et al.* further teaches that the invention of Man *et al.* "**pertains to non-polypeptide**", *i.e.*, not a protein. *See* page 1, lines 6-9 of Man *et al.* On the contrary, Tsimberidou *et al.* teaches a method of treating myeloproliferative diseases with a **protein**, *i.e.*, Etanercept (Enbrel; p75 TNFR:Fc), a **protein** comprising two naturally occurring soluble human 75-kilodalton TNF receptors linked to an Fc portion of an IgG1 (*see* Tsimberidou *et al.* at page 237, last paragraph), which clearly is **not the small molecule compound** recited in the currently amended claim 1. Further, Tsimberidou *et al.* at page 240, second full paragraph teaches that thalidomide, an isoindoline derivative, is not effective in patients with AMM. Therefore, the contradictory teachings of the cited references provide no motivation to combine so as to substitute Etanercept with the instant compound

2. The cited references would not have provided the legally required reasonable expectation of success.

The Examiner has failed to explain how one skilled in the art would have had a reasonable expectation that cyclopropanecarboxylic acid {2-[(1*S*)-1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}-amide, which is a non-polypeptide, would be effective in treating myeloproliferative disease. The Federal Circuit, following *KSR*, articulated guidelines for determining "whether the expectation of success from a particular line of inquiry is great enough to render a resulting invention obvious." (*PharmaStem*, 491 F.3d at 1364). As the Federal Circuit explained:

> [A]n invention would not be invalid for obviousness if the inventor would have been motivated to **vary all parameters or try each of numerous possible choices** until one possibly arrived at a successful result, where the prior art gave either **no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful**. Likewise, an invention would not be deemed obvious if all that was suggested was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

(*Id.* (citing *In re O'Farrell*, 953 F.2d 894, 903 (Fed. Cir. 1988))(internal quotations omitted) (emphasis added)).

In the instant case, to arrive at the instant methods, one skilled in the art have would had to try to treat "each of numerous possible choices" of disease states that can be mediated by TNF-alpha with **an isoindoline derivative**, i.e., cyclopropanecarboxylic acid {2-[(1*S*)-1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}-amide as currently claimed. Further, Tsimberidou *et al.* at page 240, second full paragraph explicitly teaches that thalidomide, an isoindoline derivative, is not effective in patients with AMM, a myeloproliferative disease. Man *et al.* is silent about myeloproliferative diseases. Therefore, none of the cited references would have provided any "indication of which parameters were critical" or any "direction as to which of [the] many possible choices is likely to be successful." As is evident from *PharmaStem*, this scenario is exactly what the Federal Circuit warned is **not** a legally sufficient "reasonable expectation of success." (*Id.*). The combination of references, at most, would have merely provided general guidance and would have merely provided a list of many disorders and a list of many compounds without any indication as to why the cyclopropanecarboxylic acid {2-[(1*S*)-1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}-amide recited in the instant claims would be specifically useful for treating the recited

myeloproliferative diseases. Thus, the cited references do not provide the requisite expectation of success, and the rejection should be withdrawn.

In view of the foregoing, Applicant respectfully requests withdrawal of the rejection of claims 1-2, 5, 10-11, 14-15 and 22-31 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* in view of Man *et al.*

IV. The Rejection of Claims 3-4 and 7-9 under 35 U.S.C. § 103(a) Should Be Withdrawn

On page 14 of the Office Action, the Examiner rejected claims 3-4 and 7-9 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* in view of Man *et al.* and Alter *et al.* (*Blood* (1985) 66:373-379). Applicant respectfully disagrees.

Claim 4 has been canceled and therefore, the rejection of claim 4 is moot. Claim 3 and 7-9 have been amended to recite, *inter alia*, a method of treating specific MPD using cyclopropanecarboxylic acid {2-[(1*S*)-1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}-amide, which was recited in claims 14-15. Applicant respectfully appreciates that claims 14-15 reciting the instant compound were not rejected. Without acquiescing to the rejection and solely to promote allowance of this case, Applicant has amended the rejected claims to recite the instant compound. Thus, this rejection is now moot and should be withdrawn.

V. The Rejection of Claim 6 under 35 U.S.C. § 103(a) Should Be Withdrawn

On page 15 of the Office Action, the Examiner rejected claim 6 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* in view of Man *et al.* and Canepa *et al.* (*British Journal of Haematology* (2001) 115:313-315). Applicant respectfully disagrees.

Claim 6 depends on claim 1 or 3. Claims 1 and 3 are amended to recite, *inter alia*, a method of treating specific MPD using cyclopropanecarboxylic acid {2-[(1*S*)-1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}-amide, which was recited in claims 14-15. Applicant respectfully appreciates that claims 14-15 reciting the instant compound were not rejected. Without acquiescing to the rejection and solely to promote allowance of this case, Applicant has amended the rejected claim to recite the instant compound. Thus, this rejection is now moot and should be withdrawn.

CONCLUSION

In light of the above amendments and remarks, the Applicant respectfully requests that the Examiner reconsider this application with a view towards allowance.

No fee is believed due for this submission. However, if any fees are required for the entry of this paper or to avoid abandonment of this application, please charge the required fees to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date: **February 12, 2009**

/Kam W. Law/

by: Kam W. Law — Reg. No. 44,205
For: Anthony M. Insogna — (Reg. No. 35,203)

Jones Day
222 East 41st Street
New York, N.Y. 10017-6702
Tel: 212-326-3778